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(71) Applicant (*for all designated States except US*): SU-CAMPO AG [CH/CH]; Graben 5, CH-6300 Zug (CH).

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(72) Inventor; and

(75) Inventor/Applicant (*for US only*): UENO, Ryuji [JP/US];
11025 Stanmore Drive, Potomac, Montgomery, MD 20854 (US).

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(74) Agents: AOYAMA, Tamotsu et al.; AOYAMA & PARTNERS, IMP Building, 3-7, Shiromi 1-chome, Chuo-ku, Osaka-shi, Osaka 540-0001 (JP).

(54) Title: COMPOSITION FOR TREATMENT OF OCULAR HYPERTENSION AND GLAUCOMA

(57) Abstract: 15-keto prostaglandin compounds containing a ring structure at the end of the omega chain are used as ocular applied intraocular pressure reducing agents. They are applied in a dose below the known dose for the corresponding 15-OH compound.

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DESCRIPTION
COMPOSITION FOR TREATMENT OF OCULAR
HYPERTENSION AND GLAUCOMA
TECHNICAL FIELD

5 The present invention relates to a composition for treatment of ocular hypertension and glaucoma.

BACKGROUND OF THE INVENTION

10 The prior art describes the use of prostaglandin analogs containing a ring structure in the omega chain for reducing intraocular pressure. A representative patent in this area is U.S. Patent 5,321,128 to Stjernschantz. These compounds contain a hydroxy group or keto group as a substituent at the 15-position. Also, one subset of these compounds contains an unsubstituted phenyl group substituted on carbon atom number 17 of the omega chain and the absence of carbons 18-20. These types of structures, where the conventional prostaglandin carbons 18-20 and their equivalent are absent are named by Stjernschantz as 18, 19,20-trinor prostaglandins.

20 One of the above-described type of compounds, latanoprost, is now sold commercially as an IOP (intraocular pressure) reducing eye drop. The clinical dosage is 1.5 μ g per dose as an eye drop, once a day. This is the U.S. FDA approved dosage. The provided liquid composition product can contain 0.005% latanoprost used

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at a dosage of one drop, or about 30 μ l, providing 1.5 μ g per dose. Latanoprost is named by Stjernschantz as 13, 14-dihydro-17-phenyl-18, 19,20-trinor-PGF₂ α isopropyl ester.

5 Another compound of this family known to date is 13,14-dihydro-15-oxo-17-phenyl- 18,19,20-trinor PGF₂ α isopropyl ester, hereinafter referred to as 15-keto latanoprost.

10 The above noted patent describes a wide potential dosage range as therapeutically active. For example, see column 5, lines 33-66 of the '128 patent ("The composition contains about 0.1-30 μ g, especially 1-10 μ g, per application of the active substance . . .") Even so, the lowest dosage used in the '128 patent for any test
15 compound for evaluating IOP reduction in humans or monkeys is 1.0 μ g per eye. For 15-keto latanoprost in the '128 patent, the tested dosage in healthy human volunteers is 5 μ g per eye and is 3 μ g in the monkey eye. Latanoprost is tested in the '128 patent at a dosage of 1.0 μ g per eye in
20 healthy human volunteers and at a dosage of 10.4 μ g in the monkey eye.

Latanoprost at its clinical concentration can cause pigmentation of the iris, a mild IOP spike and/or mild hyperemia.

25 SUMMARY OF THE INVENTION

It has been discovered that 15-keto prostaglandin compound containing a ring structure at the end of the omega chain can be used in an unusually low dosage for reduction of IOP.

5 Another embodiment of the present invention is the use of the 15-keto prostaglandin compound at a dosage up to about the therapeutically effective dosage of the corresponding 15-OH compound. The 15-keto prostaglandin compound used in the present invention does not cause
10 iridic pigmentation, an initial IOP spike nor any hyperemia at the dosages described herein.

Still another embodiment of the present invention is the use of the 15-keto prostaglandin compound for maintaining IOP reduction over an extended time following
15 an initial rapid IOP reduction brought about by another IOP reducing agent.

The embodiments of the present invention involve treatment of glaucoma where IOP reduction is needed and the lowering of IOP for purposes other than treatment of
20 glaucoma.

That is, the present invention relates to an ophthalmic composition for reducing intraocular pressure or for treating glaucoma in a mammal, which comprises a 15-keto prostaglandin compound containing a ring structure at the
25 end of the omega chain in a dose below the therapeutically

effective dose of the corresponding 15-OH compound.

In another aspect, the present invention relates to an ophthalmic composition for maintaining a reduced intraocular pressure in a mammal by periodically
5 administering the same to the mammal, which comprises an effective amount of a 15-keto prostaglandin compound containing a ring structure at the end of the omega chain.

In another aspect, the present application also relates to use of a 15-keto prostaglandin compound containing a
10 ring structure at the end of the omega chain for manufacturing the above described ophthalmic composition.

DESCRIPTION OF THE DRAWING

Figures 1 and 2 set forth the results of Example 1 comparing the employment of a dose of 0.175 μ g
15 latanoprost (Fig. 1) and the same dose of 15-keto latanoprost (Fig 2) in the monkey eye.

Figure 1 shows effect of 0.0005% latanoprost on intraocular pressure (IOP) in monkeys. Latanoprost was instilled into the right eye. The left eye received the
20 vehicle. No significant difference between the latanoprost-treated eye and the vehicle treated contralateral eye (Student's t-test)

Figure 2 shows effect of 0.0005% 15-keto-latanoprost on intraocular pressure (IOP) in monkeys. 15-keto-
25 latanoprost was instilled into the right eye. The left eye

received the vehicle. * $p < 0.05$ compared with the vehicle treated contralateral eye (Student's t-test)

Figure 3 is a graph depicting a comparison of the results for the active ingredients of Example 1 without the controls, as depicted in Figures 1 and 2. That is, Figure 3 shows effects of 0.0005% of 15-keto-latanoprost and 0.0005% latanoprost on intraocular pressure (IOP) in monkeys. ** $p < 0.01$ compared with 0.0005% latanoprost-treated group (Student's t-test).

Figure 4 depicts the results of Example 2 where an additional instillation of a small amount of latanoprost or 15-keto latanoprost is administered 12 hours after instillation of a clinical dose of latanoprost in the monkey eye. That is, Figure 4 shows effects of single installation of 0.005% latanoprost, additional instillation of 0.0005% latanoprost 12 hours after instillation of 0.005% latanoprost and additional instillation of 0.0005% 15-keto-latanoprost 12 hours after instillation of 0.005% latanoprost on intraocular pressure (IOP) in monkeys.

○ : 0.005% latanoprost alone (n=6)

□ : 0.005% latanoprost + 0.0005% latanoprost (n=6)

△ : 0.005% latanoprost + 0.0005% 15-keto-latanoprost (n=6)

(Shown as mean \pm S.E.)

* $p < 0.05$, ** $p < 0.01$ as compared with 0.005% latanoprost

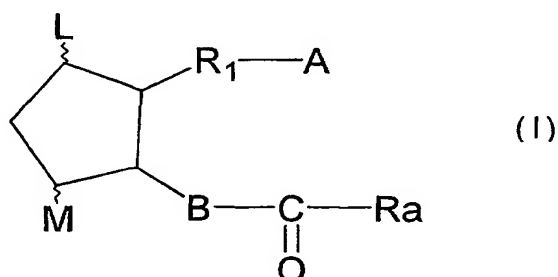
alone.

##p<0.01 as compared with 0.005% latanoprost + 0.0005% latanoprost (Turkey's comparison)

DETAILED DESCRIPTION OF THE INVENTION

5 The present invention relates to the employment of varying, including small, ocular dosages of a 15-keto prostaglandin compound containing a ring structure at the end of the omega chain as an IOP reducing agent, administered topically to the eye in the treatment of
10 glaucoma or ocular hypertension.

The preferred 15-keto prostaglandin compound of the present invention is represented by the formula (I),



15 wherein L and M are hydrogen atom, hydroxy, halogen atom, lower alkyl, lower alkoxy, hydroxy(lower)alkyl, or oxo, wherein at least one of L and M is a group other than hydrogen, and the five-membered ring may have at least one double bond;

20 A is -CH₂OH, -COCH₂OH, -COOH or a functional derivative thereof;

B is -CH₂-CH₂-, -CH=CH- or -C≡C-;

R_1 is a saturated or unsaturated bivalent lower or medium aliphatic hydrocarbon residue, which is unsubstituted or substituted with halogen, an alkyl group, hydroxy, oxo, aryl or heterocyclic group; and

5 R_a is a saturated or unsaturated lower aliphatic hydrocarbon residue, at the end of which is substituted with an aryl or aryloxy group.

In the above formula, the term "unsaturated" in the definitions for R_1 and R_a , is intended to include at least
10 one or more double bonds and/or triple bonds that are isolatedly, separately or serially present between carbon atoms of the main and/or side chains. According to the usual nomenclature, an unsaturated bond between two serial positions is represented by denoting the lower
15 number of the two positions, and an unsaturated bond between two distal positions is represented by denoting both of the positions.

The term "lower or medium aliphatic hydrocarbon" refers to a straight or branched chain hydrocarbon group
20 having 1 to 14 carbon atoms (for a side chain, 1 to 3 carbon atoms are preferable) and preferably 1 to 10, especially 1 to 8 carbon atoms for R_1 .

The term "halogen atom" covers fluorine, chlorine, bromine and iodine. Particularly preferable is a fluorine
25 atom.

The term "lower" throughout the specification is intended to include a group having 1 to 6 carbon atoms unless otherwise specified.

5 The term "lower alkyl" refers to a straight or branched chain saturated hydrocarbon group containing 1 to 6 carbon atoms and includes, for example, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, t-butyl, pentyl and hexyl.

The term "lower alkoxy" refers to a group of lower alkyl-O-, wherein lower alkyl is as defined above.

10 The term "hydroxy(lower)alkyl" refers to a lower alkyl as defined above which is substituted with at least one hydroxy group such as hydroxymethyl, 1-hydroxyethyl, 2-hydroxyethyl and 1-methyl-1-hydroxyethyl.

15 The term "lower alkanoyloxy" refers to a group represented by the formula RCO-O-, wherein RCO- is an acyl group formed by oxidation of a lower alkyl group as defined above, such as acetyl.

20 The term "cyclo(lower)alkyl" refers to a cyclic group formed by cyclization of a lower alkyl group as defined above but contains three or more carbon atoms, and includes, for example, cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl.

25 The term "cyclo(lower)alkyloxy" refers to the group of cyclo(lower)alkyl-O-, wherein cyclo(lower)alkyl is as defined above.

The term "aryl" may include unsubstituted or substituted aromatic hydrocarbon rings (preferably monocyclic groups), for example, phenyl, naphthyl, tolyl, and xylyl. Examples of the substituents are halogen atom, lower alkoxy and halo(lower)alkyl, wherein halogen atom and lower alkyl are as defined above.

The term "aryloxy" refers to a group represented by the formula ArO- , wherein Ar is aryl as defined above.

The term "heterocyclic group" may include mono- to tri-cyclic, preferably monocyclic heterocyclic group which has a 5 to 14, preferably 5 to 10 membered ring having optionally substituted carbon atom(s) and 1 to 4, preferably 1 to 3, of 1 or 2 types of hetero atoms selected from nitrogen atom, oxygen atom and sulfur atom. Examples of the heterocyclic group include furyl, thienyl, pyrrolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, imidazolyl, pyrazolyl, furazanyl, pyranyl, pyridyl, pyridazyl, pyrimidyl, pyrazyl, 2-pyrrolinyl, pyrrolidinyl, 2-imidazolinyl, imidazolidinyl, 2-pyrazolinyl, pyrazolidinyl, piperidino, piperazinyl, morpholino, indolyl, benzothienyl, quinolyl, isoquinolyl, puryl, quinazolinyl, carbazolyl, acridinyl, phenanthridinyl, benzimidazolyl, benzimidazolonyl, benzothiazolyl, phenothiazinyl. Examples of the substituent in this case include halogen, and halogen substituted lower alkyl group, wherein halogen atom and lower alkyl group

are as described above.

The term "heterocyclic-oxy group" means a group represented by the formula HcO- , wherein Hc is a heterocyclic group as described above.

5 The term "functional derivative" of A includes salts (preferably pharmaceutically acceptable salts), ethers, esters and amides.

Suitable "pharmaceutically acceptable salts" include conventionally used non-toxic salts, for example a salt with
10 an inorganic base such as an alkali metal salt (such as sodium salt and potassium salt), an alkaline earth metal salt (such as calcium salt and magnesium salt), an ammonium salt; or a salt with an organic base, for example, an amine salt (such as methylamine salt, dimethylamine
15 salt, cyclohexylamine salt, benzylamine salt, piperidine salt, ethylenediamine salt, ethanolamine salt, diethanolamine salt, triethanolamine salt, tris(hydroxymethylamino)ethane salt, monomethyl-monoethanolamine salt, procaine salt and
20 caffeine salt), a basic amino acid salt (such as arginine salt and lysine salt), tetraalkyl ammonium salt and the like. These salts may be prepared by a conventional process, for example from the corresponding acid and base or by salt interchange.

Examples of the ethers include alkyl ethers, for
25 example, lower alkyl ethers such as methyl ether, ethyl

ether, propyl ether, isopropyl ether, butyl ether, isobutyl ether, t-butyl ether, pentyl ether and 1-cyclopropyl ethyl ether; and medium or higher alkyl ethers such as octyl ether, diethylhexyl ether, lauryl ether and cetyl ether; 5 unsaturated ethers such as oleyl ether and linolenyl ether; lower alkenyl ethers such as vinyl ether, allyl ether; lower alkynyl ethers such as ethynyl ether and propynyl ether; hydroxy(lower)alkyl ethers such as hydroxyethyl ether and hydroxyisopropyl ether; lower alkoxy (lower)alkyl ethers 10 such as methoxymethyl ether and 1-methoxyethyl ether; optionally substituted aryl ethers such as phenyl ether, tosyl ether, t-butylphenyl ether, salicyl ether, 3,4-dimethoxyphenyl ether and benzamidophenyl ether; and aryl(lower)alkyl ethers such as benzyl ether, trityl ether and 15 benzhydryl ether.

Examples of the esters include aliphatic esters, for example, lower alkyl esters such as methyl ester, ethyl ester, propyl ester, isopropyl ester, butyl ester, isobutyl ester, t-butyl ester, pentyl ester and 1-cyclopropylethyl 20 ester; lower alkenyl esters such as vinyl ester and allyl ester; lower alkynyl esters such as ethynyl ester and propynyl ester; hydroxy(lower)alkyl ester such as hydroxyethyl ester; lower alkoxy (lower) alkyl esters such as methoxymethyl ester and 1-methoxyethyl ester; and 25 optionally substituted aryl esters such as, for example,

phenyl ester, tosyl ester, t-butylphenyl ester, salicyl ester, 3,4-di-methoxyphenyl ester and benzamidophenyl ester; and aryl(lower)alkyl ester such as benzyl ester, trityl ester and benzhydryl ester.

5 The amides of A mean a group represented by the
formula $-CONR'R''$, wherein each of R' and R'' is hydrogen
atom, lower alkyl, aryl, alkyl- or aryl-sulfonyl, lower alkenyl
and lower alkynyl, and include for example lower alkyl
amides such as methanamide, ethanamide, dimethanamide
10 and diethanamide; arylamides such as anilide and toluidide;
and alkyl- or aryl-sulfonylamides such as
methanesulfonylamide, ethanesulfonyl-amide and
toluenesulfonylamide.

Preferred examples of L and M include hydroxy and
15 oxo, and especially, M and L are hydroxy to provide a 5-
membered ring structure of, so called, PGF type.

Preferred A is $-COOH$, $-CH_2OH$, or its pharmaceutically acceptable salt, ester, ether or amide thereof.

20 Preferred R₁ is an unsubstituted saturated or unsaturated bivalent lower-medium aliphatic hydrocarbon residue. It may preferably have 1-10 carbon atoms, more preferably, 2-8 carbon atoms.

25 Examples of R₁ include, for example, the following
-CH₂-CH₂-,

- CH₂-CH₂-CH₂-CH₂-,
- CH₂-CH=CH-CH₂-,
- CH₂-C≡C-CH₂-,
- CH₂-CH₂-CH₂-CH₂-CH₂-,
- 5 -CH₂-CH=CH-CH₂-CH₂-,
- CH₂-C≡C-CH₂-CH-
- CH₂-CH₂-CH₂-CH₂-CH₂-CH₂-,
- CH₂-CH=CH-CH₂-CH₂-CH₂-,
- CH₂-CH₂-CH₂-CH₂-CH=CH-
- 10 -CH₂-C≡C-CH₂-CH₂-CH₂-,
- CH₂-CH₂-CH₂-CH₂-CH(CH₃)-CH₂-
- CH₂-CH₂-CH₂-CH₂-CH₂-CH₂-CH₂-CH₂-,
- CH₂-CH=CH-CH₂-CH₂-CH₂-CH₂-CH₂-,
- CH₂-CH₂-CH₂-CH₂-CH₂-CH₂-CH=CH-
- 15 -CH₂-C≡C-CH₂-CH₂-CH₂-CH₂-CH₂-,
- CH₂-CH₂-CH₂-CH₂-CH₂-CH₂-CH₂(CH₃)-CH₂-

Preferred Ra is a hydrocarbon containing 1-6 carbon atoms, more preferably, 1-4 carbon atoms, at the end of which, i.e. at the terminal of the omega chain, is substituted with an aryl or aryloxy group.

The configuration of the ring and the α- and/or ω-chains in the present invention may be the same as or different from that of the primary PGs. However, the present invention also includes a mixture of a compound

having a primary type configuration and a compound of a non-primary type configuration.

When a 15-keto-PG compound of the present invention has for example a single bond between carbon atom number
5 13 and 14, the compound may be in the keto-hemiacetal equilibrium by formation of a hemiacetal between hydroxy at position 11 and oxo at position 15.

If such tautomeric isomers as above are present, the proportion of both tautomeric isomers varies with the
10 structure of the rest of the molecule or the kind of the substituent present. Sometimes one isomer may predominantly be present in comparison with the other. However, it is to be appreciated that the compounds used in the invention include both isomers. Further, while the
15 compounds used in the invention may be represented by a structure formula or name based on keto-type regardless of the presence or absence of the isomers, it is to be noted that such structure or name does not intend to exclude the hemiacetal type compound.

20 The present invention includes any of the isomers such as the individual tautomeric isomers, a mixture thereof, or the optical isomers, a mixture thereof, a racemic mixture, and other steric isomers useful for the same purpose.

In the method of the present invention, the above-
25 described compounds are topically administered to the

affected eye 1-6 times, preferably, once or twice a day.

The ophthalmic compositions of the present invention include ophthalmic solution and ointment. The ophthalmic solution may be prepared by dissolving the active
5 ingredient into sterilized aqueous solution such as saline or buffer. A powder composition for ophthalmic solution to be dissolved before use may also be used. The ophthalmic ointment may be prepared by mixing the active ingredient with ointment base.

10 The ophthalmic vehicle employed in the practice of the present invention is that now known in the art for IOP reducing agents, such as the a-fore-mentioned latanoprost and Rescula®, the latter which has an extended omega chain providing a docosanoid classification. Additional
15 information on ophthalmic vehicles is found in the patent noted in the background section of this patent application. It is contemplated that the free acid as well as pharmaceutically acceptable salts, ethers and other esters are potentially useful in the practice of the present
20 invention, such as those described in the above-noted patent.

The 15-keto prostaglandin compound of the present invention exhibits an IOP reducing activity in a dose below the therapeutically effective dose of the corresponding 15-
25 OH compound. Further, the 15-keto prostaglandin

compound causes substantially no or less side effects including iridic pigmentation, an initial IOP spike and any hyperemia than those of the corresponding 15-OH compound. Accordingly, in the embodiment where the
5 ophthalmic composition of the present invention is to be used for reducing IOP or for treating glaucoma in a mammal, the composition contains the 15-keto prostaglandin compound in an amount which provides a dose of the 15-keto prostaglandin compound below the therapeutically
10 effective dose of the corresponding 15-OH compound.

As noted above, the clinical dose for latanoprost is about 1.5 μg per eye. At one-tenth the clinical dose, latanoprost is essentially inactive. Quite surprisingly, 15-keto latanoprost is an effective IOP reducing agent when
15 used at about one-tenth the clinical dose of latanoprost. It is contemplated in one embodiment of the present invention that the dosage range for 15-keto latanoprost as a topically applied ocular IOP reducing agent is about 0.05 to 0.75 $\mu\text{g}/\text{eye}$, preferably about 0.075 to 0.25 $\mu\text{g}/\text{eye}$, more
20 preferably about 0.1 to 0.175 $\mu\text{g}/\text{eye}$. In another embodiment of the present invention, the dosage range for 15-keto latanoprost as a topically applied ocular IOP reducing agent is about 0.05 to below 5.0 $\mu\text{g}/\text{eye}$, or about 0.1 to 4.5 $\mu\text{g}/\text{eye}$, or about 0.5 to 2.5 $\mu\text{g}/\text{eye}$, or about 1.0
25 to 2.0 $\mu\text{g}/\text{eye}$.

Other 15-keto prostaglandin compound which should be useful in the practice of the present invention are 15-oxo-16-(3-trifluoromethyl phenoxy)-17,18,19,20-tetranor $\text{PGF}_2\alpha$ and 13,14-dihydro-15-oxo-16-(3-trifluoromethyl phenoxy)-17,18,19,20-tetranor $\text{PGF}_2\alpha$ isopropyl esters. The corresponding pharmaceutically acceptable salts, ethers, other esters and amides should be useful in the practice of the present invention. See U.S. 5,510,383 for the corresponding 15-OH compound. The clinical (once a day) dosage (FDA approved dosage) for 16-(3-trifluoromethyl phenoxy)-17,18,19,20-tetranor $\text{PGF}_2\alpha$ isopropyl ester is one drop of a 0.004% solution. Drop size can range from about 20 to 50 μl , typically about 30 to 35 μl . Thus, applicant as of this writing estimates the clinical dosage of this compound to be within the range of 0.8 to 2.0 $\mu\text{g}/\text{eye}$, probably about 1.2 $\mu\text{g}/\text{eye}$. The low dosage contemplated herein for these compounds as the isopropyl ester is below 0.2 $\mu\text{g}/\text{eye}$, to as low as 0.03 $\mu\text{g}/\text{eye}$. In another embodiment of this invention, these two isopropyl ester compounds are topically applied to the eye in a dosage of about 0.05 to below 5.0 $\mu\text{g}/\text{eye}$, or about 0.1 to 4.5 $\mu\text{g}/\text{eye}$, or about 0.5 to 2.5 $\mu\text{g}/\text{eye}$, or about 1.0 to 2.0 $\mu\text{g}/\text{eye}$. In still another embodiment of this invention, the three isopropyl ester compounds disclosed herein before are topically applied in a dosage range of about 0.05 to 0.75

μg/eye, preferably about 0.075 to 0.25 μg/eye, more preferably about 0.1 to 0.175 μg/eye.

Another family of 15-keto prostaglandin compounds which should be useful in the practice of the present invention are 15-oxo-17-phenyl-18,19,20-trinor PGF₂α N-ethylamide and 13,14-dihydro-15-oxo-17-phenyl-18,19,20-trinor PGF₂α N-ethylamide. The low dosage contemplated herein for these compounds is below 15 μg/eye to as low as 0.05 μg/eye. In another embodiment of this invention, these two compounds are topically applied to the eye in a dosage of about 10μg to 0.1 μg/eye, or about 8μg to 0.5μg/eye, or about 6μg to 1 μg/eye. See U.S. 5,352,708 and U.S. 6,037,364 for the corresponding 15-OH compound, 17-phenyl-18,19,20 trinor PGF₂α N-ethylamide, which has a clinical (daily) dose (FDA approved dose) of one drop of a 0.030% solution. As of this writing the clinical dosage of this compound is not known by the applicant; however, with typical drop sizes of about 20 to 50 μl, most usually about 30 to 35 μl, the dosage is estimated at about 6 to 15 μg/eye, probably about 9 μg/eye.

In the embodiment where the ophthalmic composition of the present invention is to be used for maintaining a reduced intraocular pressure in a mammal, the dose of the 15-keto compound is not limited. The dose of the 15-keto prostaglandin compound in this embodiment may be

selected so that any side effects known for ocular application of 15-OH-prostaglandin compounds, such as iridic pigmentation, an initial IOP spike and hypermia are substantially eliminated.

5 In this embodiment, the initial rapid IOP reduction can be obtained with known IOP reducing agents, for example, Rescula®, Latanoprost, Timolol, Alphagan®, Azopt®, Cosopt®, Travoprost (isopropyl ester of fluprostenol), Bimatoprost and so on. The IOP reducing agents as above may be
10 administrated in the known or approved doses. Another alternative is to initially use a higher dose of 15-keto latanoprost, or of one of the other 15-keto compounds described herein.

 The dosages disclosed herein are for human use.

15 The ophthalmic composition of the present invention may further be admixed with any of pharmaceutically active agents in so far as said agent is compatible with the purpose of the present invention. Variations of the present invention will be apparent to the skilled artisan.

20 EXAMPLE 1

 This Example is an IOP test using the monkey eye in which about one tenth the clinical dose of latanoprost is compared in IOP reduction with the same dose of 15-keto latanoprost.

25 Summary

The intraocular pressure lowering effects of the 0.0005% solution of 13,14-dihydro-15-keto-17-phenyl-18, 19,20-trinor-PGF₂α-isopropyl ester (15-keto-latanoprost) and the 0.0005% solution of 13,14-dihydro-17-phenyl-
5 18,19,20-trinor-PGF₂α-isopropyl ester (latanoprost) were compared following a single, topical ocular instillation in monkeys.

No intraocular pressure lowering effect was noted following the instillation of 0.0005% latanoprost. On the
10 other hand, the instillation of 0.0005% 15-keto-latanoprost lowered the intraocular pressure by 2.4 mmHg 8 hours after the administration as compared with the pre-treatment value. The reduction in the intraocular pressure by the
instillation of 15-keto-latanoprost was statistically
15 significant as compared with that by the instillation of the vehicle (contralateral eye) or of 0.0005% latanoprost.

These results indicate that 15-keto-latanoprost exerts a potent intraocular pressure lowering effect with a minute dose, and suggest that 13,14-dihydro-15-keto-17-phenyl-
20 18,19,20-trinor- PGF₂α (15-keto acid of latanoprost) itself produced as a metabolite from latanoprost in the eyes participates in the reduction in the intraocular pressure after the instillation of latanoprost.

Materials and Methods

25 1. Test substance

13,14-dihydro-15-keto-17-phenyl-18,19,20-trinor-PGF₂α-
isopropyl ester (15-keto-latanoprost)

13,14-dihydro-17-phenyl-18,19,20-trinor- PGF₂α-isopropyl
ester (latanoprost,)

5 2. Preparation of dosing solutions

The solution containing 15-keto-latanoprost or
latanoprost at 0.0005% was prepared with the following
vehicle. Composition of the vehicle¹⁾ (/mL): NaCl (4.1mg),
NaH₂PO₄-H₂O (4.6mg), Na₂HPO₄-2H₂O (5.94mg),
10 Benzalkonium Chloride (0.2mg) and water for injection

3. Animals

Five male cynomolgus monkeys purchased from Kasyo
Co., Ltd. were used. These monkeys were housed
individually in cages for monkeys in a room which was
15 maintained at room temperature of 24 ± 1°C, relative
humidity of 55 ± 10%, ventilation rate of about 12
times/hour and 12-hour light-dark cycle (fluorescent
lighting: 8:00 a.m. to 8:00 p.m.). The animals were given
food pellets for monkeys (PS, Oriental Yeast Co., Ltd.),
20 vegetables and fruits, and allowed free access to tap water
from an automatic dispenser. The healthy animals without
abnormalities in the anterior segment of the eye were used
in this study.

4. Test groups and administration method

Group	Administration method	Volume of administration	n
15-keto-latanoprost 0.0005%	Instillation	35 μ L/eye	5
Latanoprost 0.0005%	Instillation	35 μ L/eye	5

Five monkeys were divided into 2 groups of the group 1 (3 monkeys) and group 2 (2 monkeys). The 0.0005% 15-keto-latanoprost and 0.0005% latanoprost were instilled into the right eye of monkeys in the group 1 and 2, respectively. One week later, 0.0005% latanoprost and 0.0005% 15-keto-latanoprost were instilled into the right eye of monkeys in the group 1 and 2, respectively, in a crossover way. Thirty-five μ L of each test solution was administered by use of a micropipet (Pipetman P 100, Gilson). To the left eye the same volume of the vehicle was administered. The intraocular pressure in each group before the instillation was as follows (in mmHg, mean \pm S.E.): the group receiving 15-keto-latanoprost; the right eye: 16.6 ± 0.5 , the left eye: 16.6 ± 0.2 , the group receiving latanoprost; the right eye: 15.8 ± 0.7 , the left eye: 17.0 ± 0.3 . There were no statistically significant differences between the values of the intraocular pressure before the instillation (Student's t-test).

5. Measurement of intraocular pressure

The animals were systemically anesthetized by an

intramuscular injection of 5 mg/kg of ketamine hydrochloride (Ketalar®50, Sankyo Co., Ltd.), and the anterior segment of both eyes was anesthetized by a instillation of 0.4% oxybuprocaine hydrochloride (Benoxil®
5 0.4% solution, Santen Pharmaceutical Co., Ltd.). The animals were fixed in a sitting position, and the intraocular pressure was measured by use of an applanation pneumatonograph (Alcon Japan Ltd.) before, and 2, 4, 8, 12 and 24 hours after the instillation. The animals were kept
10 in cages excepting the time of measurement of the intraocular pressure.

6. Statistical analysis

The data were statistically analyzed with Student's t-test. P values less than 0.05 were considered to be
15 statistically significant.

Results

The instillation of 0.0005% latanoprost did not lower the intraocular pressure (Fig. 1). On the contrary, the intraocular pressure in 0.0005% 15-keto-latanoprost-treated
20 eye was lowered by 2.4 mmHg 8 hours after the instillation as compared with the pre-treatment value, and the reduction in the intraocular pressure was statistically significant as compared with that in the vehicle-treated contralateral eye (Fig. 2). In addition, as shown in Fig. 3,
25 the reduction in the intraocular pressure with 0.0005% 15-

keto-latanoprost was also statistically significant as compared with 0.0005% latanoprost.

Discussion

In the present study, the intraocular pressure lowering effects of latanoprost and 15-keto-latanoprost in monkeys were compared following a single instillation at 0.0005%, for about one-tenth the amount of clinically used latanoprost. While no reduction in the intraocular pressure was noted following the instillation of 0.0005% latanoprost, the instillation of 0.0005% 15-keto-latanoprost significantly lowered the intraocular pressure.

Above results clearly indicate that the potency of intraocular pressure lowering effect of 15-keto-latanoprost is significantly greater than that of latanoprost. Furthermore, the fact that 15-keto-latanoprost exerted a significant intraocular pressure lowering effect at such a low concentration, at which latanoprost had no effect, strongly suggests that 15-keto acid of latanoprost, a 13,14-dihydro-15-keto-type metabolite produced from latanoprost in the eyes, participates in the intraocular pressure lowering effect after the instillation of latanoprost.

References

- 1) Sjöquist B., et al.: Drug metabolism and disposition (8): 745-754, 1998

EXAMPLE 2

This Example illustrates the employment of a low dose of 15-keto latanoprost for maintaining a low IOP level following single administration of another IOP reducing agent for obtaining a rapid drop in IOP.

Summary

The intraocular pressure in monkeys after single instillation of 0.005% latanoprost (clinical concentration) showed the maximum reduction at 12 hours after the instillation and thereafter the intraocular pressure recovered gradually and returned to the predosing level at 24 hours after the instillation. No difference was found between changes in intraocular pressure after additional instillation of 0.0005% latanoprost (the concentration: 1/10 of latanoprost 0.005%) at 12 hours after instillation of 0.005% latanoprost and those after single instillation of 0.005% latanoprost. On the other hand, when 0.0005% 15-keto-latanoprost was additionally instilled at 12 hours after instillation of 0.005% latanoprost, the intraocular pressure was significantly maintained continuously at low levels as compared with that when 0.005% latanoprost alone was instilled or that when 0.0005% latanoprost was instilled additionally at 12 hours after instillation of 0.005% latanoprost. These results suggest that 15-keto acid of latanoprost, a 13,14-dihydro-15-keto type metabolite,

produced from latanoprost in the eye after instillation of latanoprost participates in the maintenance of the intraocular pressure lowering effect after instillation of latanoprost.

5 I. Introduction

In the present study, the animals were treated by the instillation with latanoprost at the clinical concentration alone, or additional instillation of a small amount of latanoprost or 15-keto-latanoprost 12 hours after instillation
10 of latanoprost when the IOP showed the maximum reduction after instillation of latanoprost. The changes of IOP in 3 different treatment groups were compared to investigate the significance of the presence of 15-keto acid of latanoprost, a 13,14-dihydro-15-keto type metabolite, in maintaining the
15 IOP lowering effect observed after instillation of latanoprost.

II. Materials and Methods

1. Test substance

15-keto-latanoprost and latanoprost which were synthesized in Ueno Institute for Medical Science were
20 used.

2. Animals

Six male cynomolgus monkeys (body weight: 3.2 - 3.8 kg) were used. These monkeys were housed individually in cages for monkeys in a monkey rearing room which was
25 maintained at room temperature of $24 \pm 1^{\circ}\text{C}$, relative

humidity of $55 \pm 10\%$, and ventilation of about 12 times/hour and a 12-hour light-dark cycle (fluorescent lighting: 8:00 a.m. to 8:00 p.m.). The animals were given solid food for monkeys (PS, Oriental Yeast Co., Ltd.),
5 vegetables and fruits, and allowed free access to tap water from an automatic dispenser. The healthy animals without abnormalities in the anterior segment were used in this study.

3. Preparation of dosing solution

10 0.0005% and 0.005% latanoprost eye drops and 0.0005% 15-keto-latanoprost eye drops were prepared with a vehicle consisting of the following composition. The composition of the vehicles in 1 mL was as follows: sodium chloride (4.1 mg), sodium hydrogenphosphate-1H₂O (4.6
15 mg), disodium hydrogenphosphate-2H₂O (5.94 mg), benzalkonium chloride (0.200 mg) and water for injection (1 mL).

4. Administration method of test substance

In the present study, changes in IOP after instillation
20 of 0.005% latanoprost alone at the clinical concentration were compared with those in IOP after additional instillation of 0.0005% latanoprost or 0.0005% 15-keto-latanoprost 12 hours after instillation of 0.005% latanoprost to investigate the significance of the presence of a 13,14-dihydro-15-keto
25 type metabolite in maintaining the IOP lowering effect

observed after instillation of latanoprost.

The following 3 treatments were given to the right eye of monkeys at the intervals of at least 10 days. Namely, (1) instillation of 0.005% latanoprost alone, (2) additional
5 instillation of 0.0005% latanoprost at 12 hours after instillation of 0.005% latanoprost, and (3) additional instillation of 0.0005% 15-keto-latanoprost at 12 hours after instillation of 0.005% latanoprost. Thirty μ L of each test
10 substance was instilled into the right eye of animals with a Pipetman (Gilson). The same amount of the vehicle was instilled into the left eye.

5. Measurement of IOP

After the ocular surface of monkeys was anesthetized with 0.4% oxybuprocaine hydrochloride (Benoxil® 0.4%
15 solution, Santen Pharmaceutical Co., Ltd.) under i.m. systemic anesthesia with 5 - 7.5 mg/kg of ketamine hydrochloride, IOP was measured with an applanation pneumatonograph (Alcon Japan Ltd.). IOP was measured before instillation and at 4, 8, 12, 16, 20, 24, 28 and 32
20 hours after instillation of 0.005% latanoprost.

III. Results

As Fig. 4 shows, when 0.005% latanoprost alone was instilled into the eye of monkeys, IOP decreased with time at 4, 8 and 12 hours after instillation. The IOP returned
25 with time toward the predosing levels at 16 and 20 hours

after instillation of 0.005% latanoprost. IOP returned toward the predosing levels at 24 hours after instillation.

Additional instillation of 0.0005% latanoprost at 12 hours after instillation of 0.005% latanoprost did not affect IOP as compared with that after instillation of 0.005% latanoprost alone.

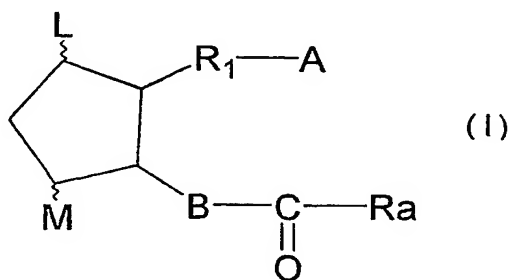
On the other hand, the IOP was maintained at significantly low levels when 0.0005% 15-keto-latanoprost was additionally instilled at 12 hours after instillation of 0.005% latanoprost as compared with that when 0.005% latanoprost alone was instilled, or that when 0.0005% latanoprost was additionally instilled 12 hours after instillation of 0.005% latanoprost.

These results indicate that the IOP lowering effect after instillation of latanoprost is prolonged markedly by additional instillation of a small amount of 15-keto-latanoprost.

CLAIMS

1. An ophthalmic composition for reducing intraocular pressure or for treating glaucoma in a mammal, which comprises a 15-keto prostaglandin compound containing a ring structure at the end of the omega chain in a dose below the therapeutically effective dose of the corresponding 15-OH compound.

2. The composition of claim 1, wherein the 15-keto-prostaglandin compound is represented by the formula (I),



wherein L and M are hydrogen atom, hydroxy, halogen atom, lower alkyl, lower alkoxy, hydroxy(lower)alkyl, or oxo, wherein at least one of L and M is a group other than hydrogen, and the five-membered ring may have at least one double bond;

A is -CH₂OH, -COCH₂OH, -COOH or a functional derivative thereof;

B is -CH₂-CH₂-, -CH=CH- or -C≡C-;

R₁ is a saturated or unsaturated bivalent lower or medium aliphatic hydrocarbon residue, which is

unsubstituted or substituted with halogen, an alkyl group, hydroxy, oxo, aryl or heterocyclic group; and

Ra is a saturated or unsaturated lower aliphatic hydrocarbon residue, at the end of which is substituted with an aryl or aryloxy group.

3. The composition of claim 1, wherein the 15-keto prostaglandin compound is 13,14-dihydro-15-keto-18,19,20-trinor-PGF₂α isopropyl ester.

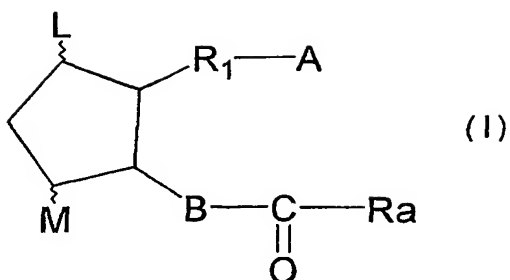
4. The composition of claim 1, wherein the dose is about one-tenth the therapeutically effective dose of the corresponding 15-OH compound.

5. The composition of claim 3, wherein the dose is about 0.05 to below 5.0μg per eye.

6. The composition of claim 1, wherein the mammal is a human.

7. An ophthalmic composition for maintaining a reduced intraocular pressure in a mammal by periodic administration to the mammal, which comprises an effective dose of a 15-keto prostaglandin compound containing a ring structure at the end of the omega chain.

8. The composition of claim 7, wherein the 15-keto-prostaglandin compound is represented by the formula (I),



Wherein L and M are hydrogen atom, hydroxy, halogen atom, lower alkyl, lower alkoxy, hydroxy(lower)alkyl, or oxo, wherein at least one of L and M is a group other than hydrogen, and the five-membered ring may have at least one double bond;

A is $-\text{CH}_2\text{OH}$, $-\text{COCH}_2\text{OH}$, $-\text{COOH}$ or a functional derivative thereof;

B is $-\text{CH}_2-\text{CH}_2-$, $-\text{CH}=\text{CH}-$ or $-\text{C}\equiv\text{C}-$;

R_1 is a saturated or unsaturated bivalent lower or medium aliphatic hydrocarbon residue, which is unsubstituted or substituted with halogen, an alkyl group, hydroxy, oxo, aryl or heterocyclic group; and

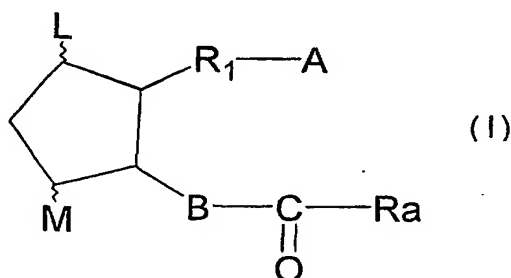
Ra is a saturated or unsaturated lower aliphatic hydrocarbon residue, at the end of which is substituted with an aryl or aryloxy group.

9. The composition of claim 7, wherein the 15-keto prostaglandin compound is 13,14-dihydro-15-keto-18,19,20-trinor-PGF 2α isopropyl ester.

10. The composition of claim 7, wherein the mammal is a human.

11. A method for reducing intraocular pressure or for treating glaucoma in a mammal which comprises topically applying to the eyes of the mammal a 15-keto prostaglandin compound containing a ring structure at the end of the omega chain in a dose below the therapeutically effective dose of the corresponding 15-OH compound.

12. The method of claim 11, wherein the 15-keto-prostaglandin compound is represented by the formula (I),



wherein L and M are hydrogen atom, hydroxy, halogen atom, lower alkyl, lower alkoxy, hydroxy(lower)alkyl, or oxo, wherein at least one of L and M is a group other than hydrogen, and the five-membered ring may have at least one double bond;

A is -CH₂OH, -COCH₂OH, -COOH or a functional derivative thereof;

B is -CH₂-CH₂-, -CH=CH- or -C≡C-;

R₁ is a saturated or unsaturated bivalent lower or medium aliphatic hydrocarbon residue, which is unsubstituted or substituted with halogen, an alkyl group, hydroxy, oxo, aryl or heterocyclic group; and

Ra is a saturated or unsaturated lower aliphatic hydrocarbon residue, at the end of which is substituted with an aryl or aryloxy group.

13. The method of claim 11, wherein the 15-keto prostaglandin compound is 13,14-dihydro-15-keto-18,19,20-trinor-PGF₂α isopropyl ester.

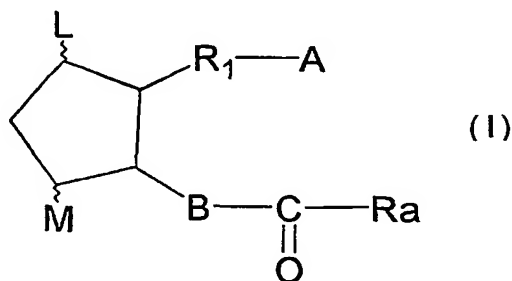
14. The method of claim 11, wherein the dose is about one-tenth the therapeutically effective dose of the corresponding 15-OH compound.

15. The method of claim 13, wherein the dose is about 0.05 to below 5.0 μg per eye.

16. The method of claim 11, wherein the mammal is a human.

17. A method for maintaining a reduced intraocular pressure in a mammal by periodically administering to the eyes of the mammal an effective amount of a 15-keto prostaglandin compound containing a ring structure at the end of the omega chain.

18. The method of claim 17, wherein the 15-keto-prostaglandin compound is represented by the formula (I),



wherein L and M are hydrogen atom, hydroxy, halogen atom, lower alkyl, lower alkoxy, hydroxy(lower)alkyl, or oxo, wherein at least one of L and M is a group other than hydrogen, and the five-membered ring may have at least
5 one double bond;

A is $-\text{CH}_2\text{OH}$, $-\text{COCH}_2\text{OH}$, $-\text{COOH}$ or a functional derivative thereof;

B is $-\text{CH}_2-\text{CH}_2-$, $-\text{CH}=\text{CH}-$ or $-\text{C}\equiv\text{C}-$;

R_1 is a saturated or unsaturated bivalent lower or
10 medium aliphatic hydrocarbon residue, which is unsubstituted or substituted with halogen, an alkyl group, hydroxy, oxo, aryl or heterocyclic group; and

Ra is a saturated or unsaturated lower aliphatic hydrocarbon residue, at the end of which is substituted with
15 an aryl or aryloxy group.

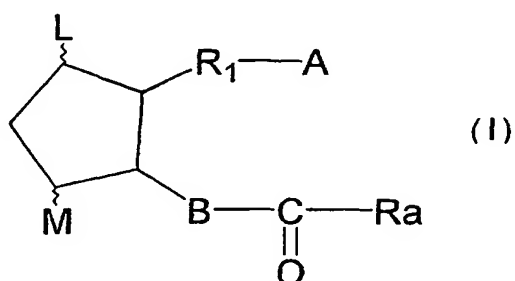
19. The method of claim 17, wherein the 15-keto prostaglandin compound is 13,14-dihydro-15-keto-18,19,20-trinor-PGF 2α isopropyl ester.

20. The composition of claim 17, wherein the mammal
20 is a human.

21. Use of a 15-keto prostaglandin compound containing a ring structure at the end of the omega chain for manufacturing an ophthalmic composition for reducing intraocular pressure or for treating glaucoma in a mammal,
25 wherein the composition comprises the 15-keto

prostaglandin compound in a dose below the therapeutically effective dose of the corresponding 15-OH compound.

22. The use of claim 21, wherein the 15-keto-prostaglandin compound is represented by the formula (I),



wherein L and M are hydrogen atom, hydroxy, halogen atom, lower alkyl, lower alkoxy, hydroxy(lower)alkyl, or oxo, wherein at least one of L and M is a group other than hydrogen, and the five-membered ring may have at least one double bond;

A is $-\text{CH}_2\text{OH}$, $-\text{COCH}_2\text{OH}$, $-\text{COOH}$ or a functional derivative thereof;

B is $-\text{CH}_2-\text{CH}_2-$, $-\text{CH}=\text{CH}-$ or $-\text{C}\equiv\text{C}-$;

R_1 is a saturated or unsaturated bivalent lower or medium aliphatic hydrocarbon residue, which is unsubstituted or substituted with halogen, an alkyl group, hydroxy, oxo, aryl or heterocyclic group; and

Ra is a saturated or unsaturated lower aliphatic hydrocarbon residue, at the end of which is substituted with aryl, aryloxy.

23. The use of claim 21, wherein the 15-keto

prostaglandin compound is 13,14-dihydro-15-keto-18,19,20-trinor-PGF2 α isopropyl ester.

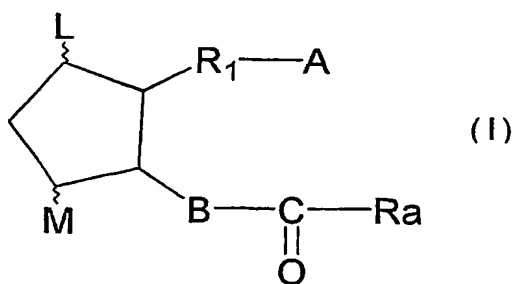
24. The use of claim 21, wherein the dose is about one-tenth the therapeutically effective dose of the corresponding 15-OH compound.

25. The use of claim 23, wherein the dose is about 0.05 to below 5.0 μ g per eye.

26. The use of claim 21, wherein the mammal is a human.

27. Use of a 15-keto prostaglandin compound containing a ring structure at the end of the omega chain for manufacturing an ophthalmic composition for maintaining a reduced intraocular pressure in a mammal, which is to be administrated periodically to the mammal.

28. The use of claim 27, wherein the 15-keto-prostaglandin compound is represented by the formula (I),



Wherein L and M are hydrogen atom, hydroxy, halogen atom, lower alkyl, lower alkoxy,

hydroxy(lower)alkyl, or oxo, wherein at least one of L and M is a group other than hydrogen, and the five-membered ring may have at least one double bond;

A is $-\text{CH}_2\text{OH}$, $-\text{COCH}_2\text{OH}$, $-\text{COOH}$ or a functional
5 derivative thereof;

B is $-\text{CH}_2-\text{CH}_2-$, $-\text{CH}=\text{CH}-$ or $-\text{C}\equiv\text{C}-$;

R_1 is a saturated or unsaturated bivalent lower or medium aliphatic hydrocarbon residue, which is unsubstituted or substituted with halogen, an alkyl group,
10 hydroxy, oxo, aryl or heterocyclic group; and

R_a is a saturated or unsaturated lower aliphatic hydrocarbon residue, at the end of which is substituted with an aryl or aryloxy group.

29. The use of claim 27, wherein the 15-keto
15 prostaglandin compound is 13,14-dihydro-15-keto-18,19,20-trinor-PGF 2α isopropyl ester.

30. The use of claim 27, wherein the mammal is a human.

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Fig. 1

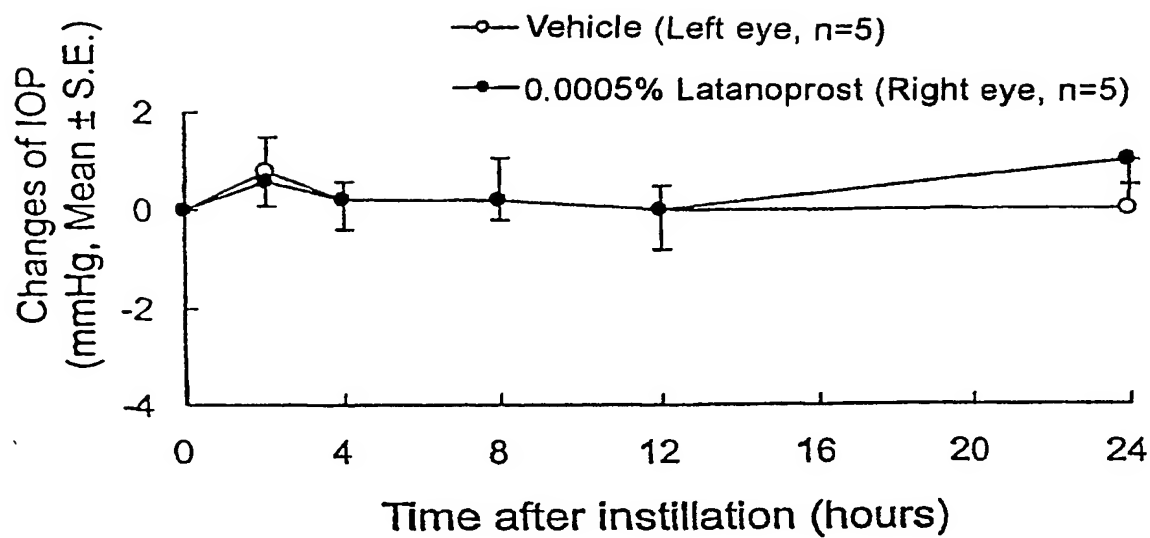
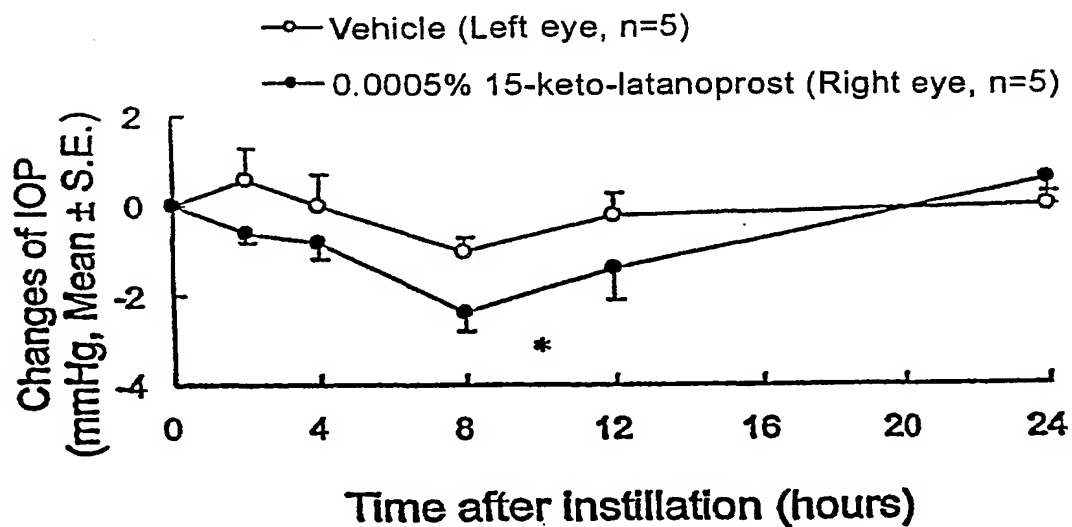


Fig. 2



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Fig. 3

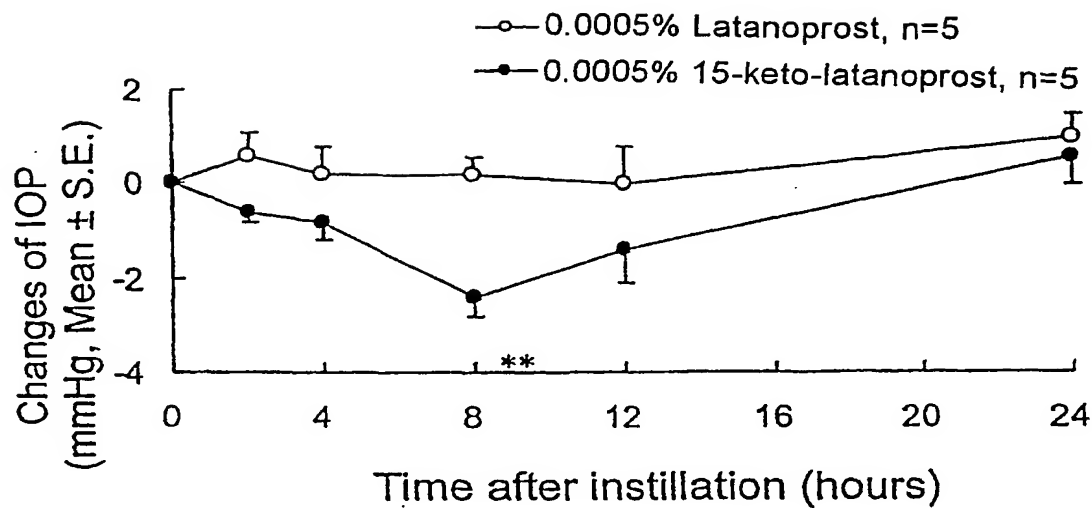


Fig. 4

